

Multi-component synthesis of spiro[indoline-3,4'-pyrrolo[3,4-c]pyrazoles] using Zn(BDC) metal-organic frameworks as a green and efficient catalyst

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Abstract

In this research, a series of spiro compounds was efficiently synthesized *via* one-pot multi component reactions of isatins, aryl amines, dimethyl acetylenedicarboxylate and hydrazine in the presence of Zn(BDC) MOF as catalyst. The key superiorities of this process are high yields, easy work-up, short reaction times, and purification of the products by the non-chromatographic system. The study of the reusability of the catalyst showed that the Zn(BDC) can be readily recovered and reused six times with a slight decrease in its activity. Furthermore, the catalyst was characterized by SEM, EDX, FT-IR and XRD analysis.

Keywords: Multi-component reaction; metal-organic framework; pyrrole; Zn (BDC); catalyst.

Introduction

Five-membered heterocycles bearing one heteroatom are very wide in nature and are known for their diverse biological properties [1]. Pyrrole ring is one of the most important heterocyclic compounds that are involved in many natural compounds of various chemicals and drugs such as porphyrins, globulins and vitamins [2]. Pyrrole would also have significant properties including antioxidant, anti-inflammatory, anti-tumor, and antibacterial agent [3]. Given the importance of heterocyclic compounds in the chemical structure of drugs, researchers in many parts of the world examine the synthesis of new heterocyclic rings and attach them to different chemical agents, specific drug

effects, and sometimes new drug effects [4,5]. So far, the pyrrole derivatives have been synthesized using several different multi-component reactions [6]. One such reaction was a Paal-Knorr reaction, in which the 2, 5-dimethoxytetrahydrofuran reacted with the amines and sulfonamines in water in the presence of Iron (III) chloride [7]. Moreover, the reaction of carboxylic acid with 2, 4, 4-trimethyl butan-1 amines and 1, 3-dienyl boronic esters was afforded pyrrole derivatives [8]. The reaction between diols and triols in the presence of sodium chloride effectively synthesized the pyrroles [9]. Metal-organic frameworks (MOFs) are a new category of heterogeneous catalysts consisting of two metal ion units as nodes and

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organic units as connectors [10]. The high surface, selectivity, porosity and flexibility which are the hallmarks of this catalyst have attracted chemists to research and use this catalyst [11]. MOFs can be used as catalyst [12], gas storage [13] and separation of gases [14], water and wastewater treatment [15] and removal of pollutants [16], as well as the production of light weight buildings [17].

In our continuation to develop efficient, environmentally friendly, inexpensive, and economical

approaches for the synthesis of different heterocyclic compounds, we have synthesized various biologically interesting products using nanocatalysts [18-21].

Hence, a new protocol using Zn(BDC) (Figure 1) as a highly effective nano-porous material is reported for the preparation of pyrrole derivatives *via* the four-component reaction of isatins, aryl amines, dimethyl acetylenedicarboxylate and hydrazine in water/ethanol as solvent (Scheme 1).

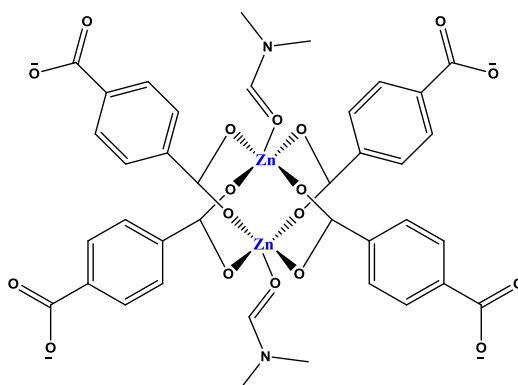
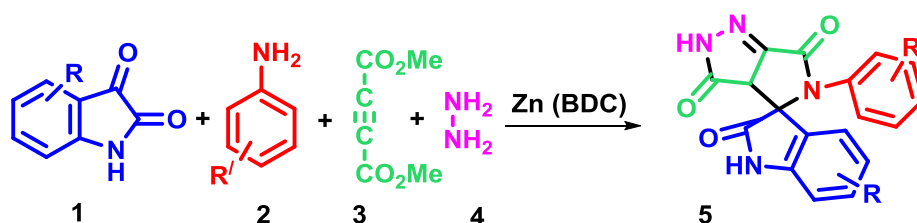


Figure 1. Structure of Zn(BDC) MOF



Scheme 1. Synthesis of spiro[indoline-3,4'-pyrrolo[3,4-c]pyrazoles] by Zn(BDC) as catalyst

Experimental

Materials and Instrumentation

Chemicals were purchased from the Sigma-Aldrich and Merck in high purity. All melting points are uncorrected and determined in capillary tube on Boetius melting point microscope. ^1H NMR and ^{13}C NMR spectra were obtained on Bruker 400 MHz spectrometer with CDCl_3 as solvent using TMS as an internal

standard. FT-IR spectrum was recorded on Magna-IR, spectrometer 550. The elemental analyses (C, H, N) were obtained from a Carlo ERBA Model EA 1108 analyzer. Powder X-ray diffraction (XRD) was carried out on a Philips diffractometer of X'pert Company with mono chromated Cu $\text{K}\alpha$ radiation ($\lambda = 1.5406 \text{ \AA}$). Microscopic morphology of products was visualized by SEM (LEO 1455VP).

The mass spectra were recorded on a Joel D-30 instrument at an ionization potential of 70 eV. The compositional analysis was done by energy dispersive analysis of X-ray (EDX, Kevex, Delta ClassI).

Preparation of Zn(BDC) MOF

The equimolar quantities of zinc nitrate hexahydrate (0.596 g, 2 mmol) and terephthalic acid (0.332 g, 2 mmol) were dissolved in 30 mL DMF. This solution was placed in a closed flask in an oven at 100 °C for 12 h. The colorless cubic crystals were filtered and washed with 100 mL DMF solution. The filtered material was immersed in chloroform after an exchange with DMF solution for 24 h [22-25].

Synthesis of spiro[indoline-3,4'-pyrrolo[3,4-c]pyrazole] derivatives

A mixture of isatin (1.0 mmol), anilines (1.0 mmol), hydrazine (2.0 mmol) and dimethyl acetylene dicarboxylate (2.2 mmol), Zn (BDC) (0.01 g) in water/ethanol (10 mL, molar ratio 1:1) was stirred at 50 °C temperature. After completion of the reaction as determined by thin layer chromatography (TLC), the obtained residue was dissolved in methanol. The catalyst was insoluble in methanol and was separated by simple filtration. The solvent was evaporated and the residue was recrystallized from ethanol to afford the pure product.

Spectral data of the some products

5'-(4-Methoxyphenyl)-2',3a'-dihydro-3'H-spiro[indoline-3,4'-pyrrolo[3,4-c]pyrazole]-2,3',6'(5'H)-trione (5a)

Orange Solid; m.p. 191-193 °C; ¹H NMR (400 MHz, CDCl₃) δ ppm: 3.59 (1H, CH), 3.84 (3H, OCH₃), 6.42-7.32 (8H, m, Ar-H), 10.51 (1H, NH), 12.5 (1H, NH); FT-IR (KBr): 3230 (NH), 2952 (CH), 1733, 1724 (C=O), 1512 (

C=N), 1441 (C=C), 1038 (O-C) cm⁻¹. Anal. Calcd. For C₁₉H₁₄N₄O₄: C 62.98, H 3.89, N 15.46. Found C 62.89, H 3.79, N 15.34. MS (EI) (m/z): 362 (M⁺), 331 (M-15, 65%), 303 (M-48, 43%).

5'-(4-Chlorophenyl)-2',3a'-dihydro-3'H-spiro[indoline-3,4'-pyrrolo[3,4-c]pyrazole]-2,3',6'(5'H)-trione (5b)

Orange Solid; m.p. 211-213 °C; ¹H NMR (400 MHz, CDCl₃) δ ppm: 3.63 (1H, CH), 7.15-7.85 (8H, m, Ar-H), 10.58 (1H, NH), 12.2 (1H, NH); FT-IR (KBr): 3269-3438 (NH), 2922(CH), 1739, 1722, (C=O); 1610 (C=N) cm⁻¹. Anal. Calcd. For C₁₈H₁₁ClN₄O₃: C 58.95, H 3.02, Cl 9.67, N 15.28. Found C 58.83, H 3.19, Cl 9.57, N 15.14. MS (EI) (m/z): 369 (M⁺), 333 (M-36, 56%).

5-Nitro-5'-(4-nitrophenyl)-2',3a'-dihydro-3'H-spiro[indoline-3,4'-pyrrolo[3,4-c]pyrazole]-2,3',6'(5'H)-trione (5h)

Solid Orange; m.p. 273-276 °C; ¹H NMR (400 MHz, CDCl₃) δ: ppm: 1.91 (1H, CH), 6.99-7.04 (3H, Ar-H), 7.92(1H, NH), 8.07-8.17 (4H, Ar-H), 9.46 (1H, NH); FT-IR (KBr): 3398-3288 (NH), 1743 (N-C=O), 1616 (C=N), 1469-1504 (C=C) cm⁻¹. Anal. Calcd. For C₁₈H₁₀ N₆O₇: C 51.19, H 2.39, N 19.90. Found C 51.11, H 2.47, N 19.98. MS (EI) (m/z): 422 (M⁺), 351 (M-26, 51%), 331 (M-46, 28%).

Results and discussion

In the preliminary experiments, Zn (BDC) MOF were synthesized and analyzed using EDX, FE-SEM, FTIR and XRD analysis. The chemical purity of the samples as well as their stoichiometry was tested by EDX study. The EDX spectrum which is given in Figure 2 shows the presence of zinc, carbon and oxygen as the only elementary components.

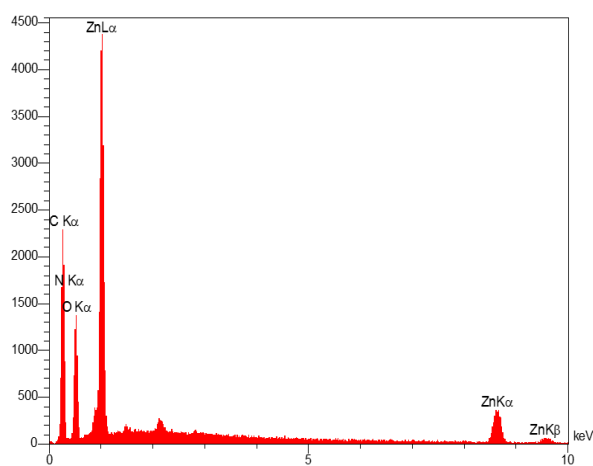


Figure 2. EDX spectrum of Zn(BDC)

In order to investigate the morphology and particle size of the prepared Zn (BDC) metal organic framework, SEM image of the nanocatalyst was presented in Figure 3. The, Zn (BDC) MOF is probably an

impure crystal phase with an irregular shape as shown in the SEM photo. This may be caused by the multiple coordination modes in the Zn-MOF crystals that formed the multiple structures.

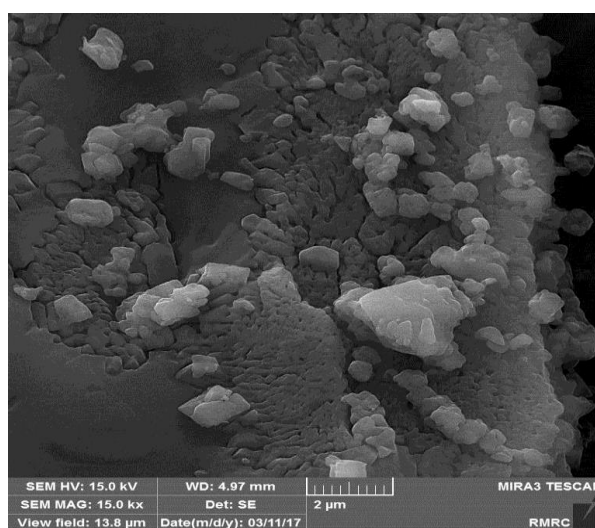


Figure 3. SEM image of Zn (BDC) MOF

The FT-IR spectrum of the Zn (BDC) catalyst is presented in Figure 4. Asymmetric and symmetric stretching vibrations of -COO^- are appeared at

1668 and 1388 cm^{-1} . In addition, the revealed bands at 1628 and 1504 cm^{-1} are related to C=C of the aromatic rings.

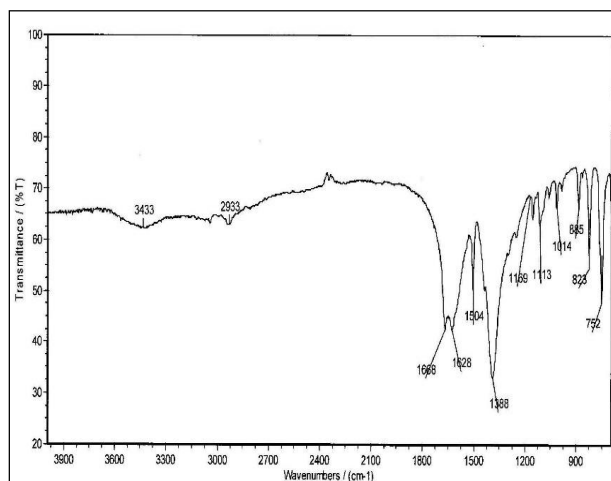


Figure 4. The FT-IR spectrum of Zn (BDC) MOF

The strong XRD intensity of the peak at 9.8° demonstrates that many of the crystal faces at (220) were formed in the Zn (BDC) MOF (Figure 5). The weak XRD intensity of the three theta peaks at 15.5° , 16.8° , and 20.8° reveals a few crystal faces at (400), (420), and (531), respectively, in Zn (BDC) MOF. The lack of some crystal faces indicates

that the morphology of Zn (BDC) MOF is a random slab of a certain thickness rather than a cubic crystal. The Zn (BDC) MOF is probably an impure crystal phase with an irregular shape as shown in the SEM photo. This may be caused by the multiple coordination modes in the Zn-MOF crystals that formed the multiple structures.

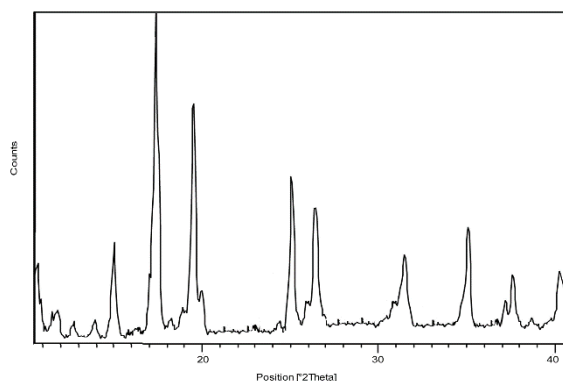


Figure 5. XRD pattern of Zn (BDC) MOF

In continuation of this research and in order to explore and optimize the various reaction conditions, we selected a multi-component reaction of isatin, 4-methoxyaniline, dimethyl acetylene dicarboxylate and hydrazine as a model reaction (Scheme 2).

Initially, to show the advantage of our approach in comparison to other catalysts, we compared the reactions of the different nanocatalysts (0.01 g of

each catalyst) including MgO, ZnO, CuO and Fe₃O₄ with Zn(BDC) in the synthesis of 5'-(4-methoxyphenyl)-2',3a'-dihydro-3'H-spiro[indoline-3,4'-pyrrolo[3,4-c]pyrazole]-2,3',6'(5'H)-trione (**5a**).

As shown in Table 1, Zn (BDC) metal organic framework is the best catalyst with respect to reaction times and yields of the products.

Table 1. The model reaction by various catalysts

Entry	Catalyst	Time(min)	Yield (%)
1	Fe ₃ O ₄	240	75
2	MgO	360	55
3	ZnO	200	80
4	CuO	240	70
5	Zn(BDC)	180	95

Reaction conditions: The mixture of each reaction was heated at 50 °C in ethanol.

Also, the model study was carried out in the presence of different solvents such as ethanol, dichloromethane, toluene and water/ethanol, methanol and also solvent-

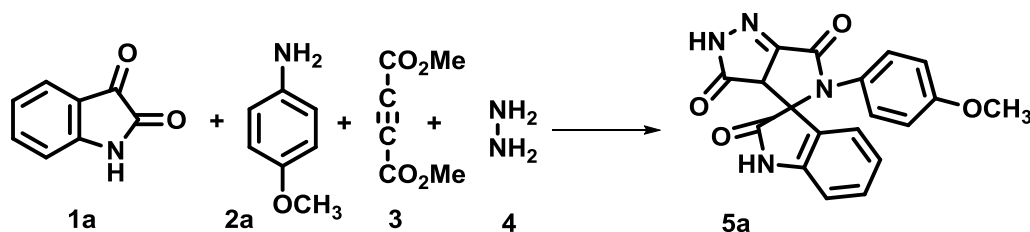
free conditions. The summarized results of Table 2 show that the best results were obtained in water/ethanol as solvent at 50 °C (Table 2).

Table 2. Screening of solvents in the model reaction

Entry	Solvent	Time (min)	Yield (%)
1	C ₂ H ₅ OH(50°C)	180	95
2	PhCH ₃ (50°C)	360	45
3	CH ₂ Cl ₂ (50°C)	300	55
4	H₂O/ C₂H₅OH(50°C)	180	95
5	CH ₃ OH(50°C)	240	70
6	solvent-free(100°C)	300	75

In this research, we have continued to use Zn (BDC) as the catalyst in the synthesis of a variety of pyrrole derivatives (Scheme 1). As shown in the Table 3, spiro[indoline-3,4'-pyrrolo[3,4-c]pyrazole] derivatives

were synthesized using different isatins and anilines. It was found that aryl amines with electron-donating groups reacted faster than anilines with electron-withdrawing groups.



Scheme 2. The model reaction for the synthesis of 5'-(4-methoxyphenyl)-2',3a'-dihydro-3'H-spiro[indoline-3,4'-pyrrolo[3,4-c]pyrazole]-2,3',6'(5'H)-trione (**5a**)

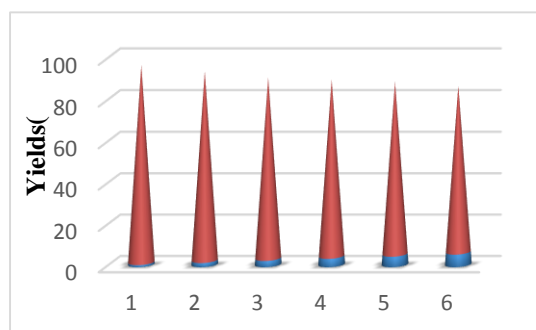
Table 3. Synthesis of spiro[indoline-3,4'-pyrrolo[3,4-c]pyrazoles] by Zn(BDC)

Entry	Isatin	Aniline	Product	Time (min)	Yield (%)	M.p. (°C)
1	H (1a)	4-OCH ₃ (2a)	5a	180	95	191-193
2	H (1a)	4-Cl (2b)	5b	220	92	211-213
3	5-NO ₂ (1b)	4-Cl (2b)	5c	200	90	224-227
4	5-NO ₂ (1b)	4-CH ₃ (2c)	5d	200	92	206-208
5	5-NO ₂ (1b)	4-OCH ₃ (2a)	5e	160	88	261-262
6	H (1a)	4-CH ₃ (2c)	5f	200	90	186-187
7	H (1a)	4-NO ₂ (2d)	5g	240	95	204-205
8	5-NO ₂ (1b)	4-NO ₂ (2d)	5h	220	91	273-276

Recycling and reusing of the catalyst

The reusability of the Zn(BDC) was studied by repeating the model study using the recovered catalyst under

optimized reactions. It was concluded that the Zn(BDC) nanostructure could be reused six times with a slightly decrease in its activity (Figure 6).

**Figure 6.** Reusability of the Zn(BDC)

Conclusion

We successfully developed a facile, green and efficient method for multi-component synthesis of spiro[indoline-3,4'-pyrrolo[3,4-c]pyrazole derivatives by the reaction of isatins, anilines, dimethyl acetylene dicarboxylate and hydrazine in the presence of Zn (BDC) as the catalyst in water/ ethanol. The products were obtained in excellent yields within short reaction times. Moreover, Zn (BDC) metal organic framework had significant advantages such as economical, recoverability, reusability and stability.

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